Cell

Muscle

As New Year's resolutions fall slowly by the wayside and those jogging shoes gather dust, this issue's Select gives you the motivation to keep going with two new papers that reveal the benefits of exercise. We also join the debate about the cause of a common form of muscular dystrophy and find out why, for some individuals (and mice), the heat of a workout could spell sudden death.

The Greek goddess Iris.

From: Muscle. You Have One New Message

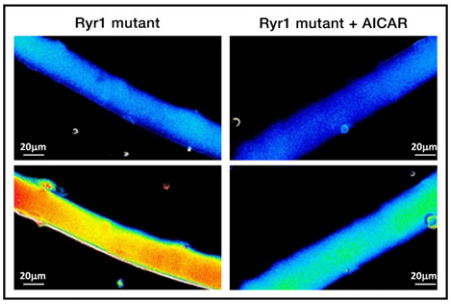
The long-term benefits of exercise for the muscular system are relatively well understood. In mice, active muscles turn on a program of gene expression driven by the transcription factor PGC1-α, which boosts production of mitochondria and encourages the formation of new blood vessels, increasing the muscle's ability to respond to increased workload. However, exercise also promotes a host of other changes across the whole body that are more difficult to explain. In fact, simply increasing expression of PGC1-α in mouse muscle is sufficient to induce many of these changes, including enhanced resistance to both diabetes and age-related obesity and extended lifespan. How is it that the musculature can exert such a powerful global influence on metabolism? Boström et al. (2012) now identify a new hormone that is released by muscle under conditions of regular exercise. The hormone, which they named irisin after the Greek messenger goddess Iris, acts on subcutaneous fat deposits to stimulate energy consumption. It does this by causing white fat cells to take on characteristics of thermogenic brown fat. Brown adipose tissue expends energy by metabolizing lipid and glucose to generate heat rather than ATP. This presents a paradox: what is the benefit of wasting energy to generate heat in conditions in which ATP demand due to exercise is increased? It is possible that the mechanism originally evolved as a response to the cold; muscle activity from shivering would trigger additional heat production from the adipose tissues.

The effect of irisin on energy consumption may, however, have an unexpected payoff for modern humans. "Browning" of white adipose tissue by genetic manipulation of the differentiation program has previously been shown to improve glucose homeostasis, so the authors tested whether injecting mice with a viral vector carrying the irisin gene would have a similar effect. Remarkably, even though these mice display relatively modest increases in circulating irisin levels, the treatment significantly improves glucose tolerance in mice fed a high-fat diet. Their results raise hopes that the hormone may provide therapeutic benefits for the treatment of type II diabetes and obesity in humans and could be particularly valuable for patients who are otherwise unable to exercise. It remains to be discovered how irisin signals to its target cells, but identification of the irisin receptor may be the next step toward identifying other target tissues for this exciting new hormone.

Boström, P., et al. (2012). Nature 481, 463–468.

Keep Cool and Carry On

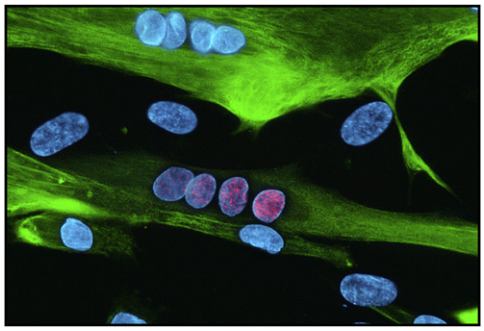
Burning off excess calories at the gym may be a great idea for many reasons, but that might not be the case if you're one of the rare individuals with a genetic susceptibility to heat stroke or malignant hyperthermia, a condition that renders sufferers hypersensitive to extremes in temperature and exposure to inhalation anesthetics. In some individuals, exposure to these triggers can result in a potentially fatal collapse of the muscular system, characterized by whole-body contractions and breakdown of muscle fibers. Malignant hyperthermia belongs to a family of diseases caused by mutations in the ryanodine receptor gene, RYR1. Affected individuals are often identified only by chance in the operating theater upon being treated with general anesthetics. In these circumstances, the symptoms can be readily reversed by rapid administration of the muscle relaxant dantrolene. If the response is triggered by elevated environmental temperatures, however, the cause of collapse may not be identified until it is too late. Thus, there is considerable interest in identifying drugs that could prevent the attacks from occurring in the first place.



Fura-2 imaging reveals resting Ca^{2+} levels in muscle fibers of Ryr1 mutant mice. AICAR (right) prevents high temperature-induced calcium influx (bottom).

Using a mouse model of malignant hyperthermia carrying a Ryr1 mutation equivalent to that found in the human disease, Lanner and coworkers identify a candidate prophylactic treatment for enhanced susceptibility to heat stroke. Heterozygous mutant mice die suddenly with heat stroke-like symptoms when exposed to temperatures above 37°C or when exercising at temperatures above 25°C. Strikingly, mice treated with the AMP mimic AICAR are protected. AICAR is perhaps best known as an activator of the metabolic enzyme AMPK, but in this case, the authors rule out a role for AMPK in prevention of heat-induced response. Instead, AICAR seems to act directly on the mutant ryanodine receptor, plugging a calcium leak that

could underlie the patients' sensitivity to heat. AICAR has previously been reported to behave as an exercise mimetic that enhances muscle performance and thus may be an excellent candidate for future clinical investigation.
Lanner, J.T., et al. (2012). Nat. Med. Published online January 8, 2012. 10.1038/nm.2598.



Cultured FSHD skeletal muscle shows a rare burst of DUX4 protein expression (red) in the nucleus of a myofiber (blue DAPI, green myosin). Photograph by Linda Geng.

Muscular Dystrophy Gene DUX Detection

In a world of complex diseases, whole-genome sequencing, and genome-wide association studies, you could be forgiven for thinking that the cataloging of humanity's monogenic disorders will soon be relegated to the work of undergraduate students and robots. But the identification of disease genes is not always simple. The mutation that causes one of the most common forms of muscular dystrophy, fascioscapulohumeral dystrophy (FSHD), was first identified nearly 20 years ago. But since then, identifying the gene whose expression is modified by this mutation has proven to be more challenging. The most common variant of the disease, FSHD1, is associated with loss of a chunk of subtelomeric macrosatellite repeats: affected individuals tend to have fewer than 10 of these repeats remaining, whereas unaffected individuals may have as many as 100 in the same location. Each repeat contains a single copy of the DUX4 retrogene, and because deletion of repeats was shown to be associated with decreased levels of repressive epigenetic marks in the region, it has been proposed that inappropriate expression of this transcription factor is responsible for FSHD1. However, DUX4 mRNA is not reliably detected in FSHD muscle, leading many to focus on other genes in the region as potential disease candidates.

Geng et al. (2012) now provide evidence that DUX4 may, in fact, be the gene responsible after all. Rather than look for expression of DUX4 itself, they reasoned that detection of its downstream transcriptional targets might provide a more sensitive readout for DUX4 activity. They identify a cohort of genes with DUX4-binding sites that are upregulated in myoblasts expressing DUX4 and find that the same cohort of genes displays elevated expression in FSHD muscle cultures and biopsies compared with cultures and biopsies derived from unaffected individuals. Not only do the findings support a role for DUX4 activity in FSHD pathology, they also provide some insight into the downstream consequences of DUX4 expression. DUX4 targets are enriched in genes associated with the germline and innate immunity, and it will be interesting to test whether these targets play any role in the immunopathology that can accompany FSHD.
Geng, L.N., et al. (2012). Dev. Cell 22, 38–51.

Exercising Autophagy

The treadmill route to boosting autophagy.

Hungry cells are well known to resupply their dwindling reserves of energy by digesting their intracellular contents, enclosing whole swathes of cytoplasm and organelles in a double-membrane structure, the autophagosome, which is delivered to the lysosome for destruction. Recent years have demonstrated that autophagy, rather than acting as a simple waste disposal system, plays an integral part in cellular homeostasis, serving a generally protective function in diabetes, cancer, infection, and neurodegenerative disease. Recent work by He et al. (2012) now extends the repertoire of autophagy to include an important role in mediating some of the beneficial effects of exercise. In mice trained on a treadmill, exercise promotes autophagy not only in muscle, but also in a number of other tissues, including liver and pancreas.

To test the function of this widespread upregulation, they constructed a mutant mouse that exhibits normal levels of basal autophagy but is unable to upregulate autophagy in response to physiological triggers such as starvation. This was achieved by inactivating three phosphorylation sites in the BCL2 gene. The resulting BCL2-AAA mice are viable and fertile and have histologically normal muscles, but they fail to display increased autophagy in response to exercise. In the absence of exercise-induced autophagy, the mice are less able to endure sustained physical exertion, and unlike control mice, their muscles do not respond to exercise by increasing plasma membrane targeting of the glucose uptake channel GLUT4. Most tellingly, although feeding with a high-fat diet impairs glucose tolerance and increases levels of serum triglycerides and cholesterol to a similar extent in both the BCL2-AAA mice and the corresponding controls, these impairments are countered by exercise in control animals, but not in the mutants. Although additional effects of the BCL2-AAA mutation can't be ruled out, it therefore seems likely that exercise-induced autophagy is required to mediate the beneficial effects of physical exertion on metabolism. How it does this remains a mystery that will no doubt exercise the minds of those in the Levine lab and beyond.
He, C., et al. (2012). Nature 481, 511–515.

Niki Scaplehorn